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**EDITORIAL**

# Platelet glycoprotein IIb/IIIa receptor inhibitors—end of an era?

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**This editorial refers to 'One-year clinical outcomes with abciximab vs. placebo in patients with non-ST-segment elevation acute coronary syndromes undergoing percutaneous coronary intervention after pre-treatment with clopidrogel: results of the ISAR-REACT-2 randomized trial' by G. Ndrepepa *et al.*,[†] on page 455**

The second Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT-2) study randomized 2022 high-risk patients with non-ST-segment elevation acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI) to receive abciximab or placebo in addition to aspirin and clopidogrel 600 mg loading dose administered at least 2 h prior to the procedure. All patients received periprocedural unfractionated heparin. The incidence of the primary end-point of the study—the composite of death, myocardial infarction (MI), or urgent target vessel revascularization (TVR) at 30 days—was significantly reduced by 25% in the abciximab group.[1] No difference was observed in terms of major or minor bleeding events between treatment assignments. In the present issue of the journal, Ndrepepa *et al.* have demonstrated that a statistically significant benefit is maintained at 1 year, with a 20% reduction in the rate of death, MI, or TVR, and a 25% reduction in death or MI among patients allocated to abciximab.[2] Despite the positive results, it seems unlikely that these findings will translate into an increase in the prescription of platelet glycoprotein IIb/IIIa receptor inhibitors (GP IIb/IIIa inhibitors). The use of this drug class has declined substantially since the advent of clopidogrel, and now GP IIb/IIIa blockers have to compete with newer antithrombotic and antiplatelet agents such as bivalirudin, fondaparinux, and prasugrel.

The GP IIb/IIIa receptor—or αIIB/β3 integrin—is the most abundant platelet membrane glycoprotein found in humans and is a key mediator of thrombus formation. Following spontaneous rupture of an atherosclerotic plaque or balloon catheter-mediated barotrauma of the vessel wall, the subendothelial matrix is exposed to the blood circulation. Substances such as collagens, fibronectins, and von Willebrand factor (vWF) are recognized by adhesion receptors on the platelet surface and promote platelet adhesion and activation. The hallmark of platelet activation is the conformational changes of the GP IIb/IIIa receptor—with subsequent transformation from a low- into a high-affinity state—allowing for binding of fibrinogen and vWF.[3] Although GP IIb/IIIa antagonists achieve a greater degree of platelet aggregation inhibition than aspirin or clopidogrel they do not affect platelet activation but primarily inhibit platelet aggregation by competing with ligand binding, a critical step for interplatelet bridging and aggregate formation. The excitement that accompanied the launch of GP IIb/IIIa blockers in the 1990s was based on the assumption that the inhibition of the 'final common pathway' of platelet aggregation would translate into an improvement in prognosis of patients undergoing PCI or presenting with ACS. Abciximab, the prototype of the GP IIb/IIIa blockers, contributed much to the aura surrounding this drug class. Key to success were the unmatched degree of platelet aggregation inhibition achieved—approximately 95% at 5 min after intravenous bolus administration—and also the interest surrounding its peculiar molecular structure—a fragment of a mouse–human chimeric monoclonal antibody.

The clinical testing phase started with the three EPI trials in which abciximab was administered against placebo in patients undergoing PCI. The studies included patients with stable and unstable coronary disease. Stenting was performed in a minority of patients, and ADP antagonists were administered only in stented patients following the procedure.[4] Subsequently, other compounds of the same class—tirofiban, eptifibatide, and lamifiban—entered randomized trial evaluation. The benefit associated with the use of these agents was mainly in terms of reduction in periprocedural MI, though from the very beginning a controversy surrounded the clinical relevance of the differences observed in post-procedural elevation of cardiac enzymes. With respect to long-term benefit, a pooled analysis of the EPI trials reported that the administration of abciximab was associated with a mortality reduction at 4.8 years follow-up.[3] The last GP IIb/IIIa inhibitor–PCI trial performed without a systematic clopidogrel loading dose prior to the procedure was the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT)

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study, in which allocation to the GP IIb/IIIa receptor inhibitor eptifibatide in a novel dosing (double bolus) was associated with a 35% reduction in death, MI, or urgent TVR at 30 days among patients undergoing coronary stenting.[5] For the first time, approximately half of the patients were pre-treated with a thienopyridine (either ticlopidine or clopidogrel) in addition to aspirin.

In parallel to the PCI setting, the efficacy of GP IIb/IIIa inhibitors was tested in the medical management of non-ST-segment elevation ACS. Overall, the use of these agents resulted in a modest benefit over placebo despite no use of clopidogrel, namely a 9% relative reduction in death or MI at 30 days.[6] In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) IV study, abciximab was even harmful if administered over a 48 h period.[7] As a consequence of insufficient efficacy, the compound lamifiban was abandoned. The confidence in GP IIb/IIIa inhibitors was further shaken by the premature termination of clinical trials testing of prolonged oral GP IIb/IIIa blockade post-ACS because of the increased mortality rate in the active treatment arm.[8] Although the underlying mechanisms remain to be demonstrated, a prothrombotic state associated with chronic insufficient platelet inhibition was postulated.[9]

It has been difficult to integrate the results of GP IIb/IIIa studies from the 1990s into a contemporary setting characterized by clopidogrel loading, newer anticoagulants, and varying degrees of patient acuity and risk/benefit. By means of three sequential randomized trials, the group of Schömig and Kastrati in Munich systematically addressed the issue of whether GP IIb/IIIa receptor inhibitors conferred additional benefit in low-, medium-, and finally high-risk patients undergoing PCI following optimal pretreatment with clopidogrel (i.e. with 600 mg at least 2 h prior to the procedure). The ISAR-REACT study enrolled stable patients and detected no benefit of GP IIb/IIIa blockade. The patients enrolled were at low risk, with a death, MI, or urgent TVR rate at 30 days of 4%.[10] Subsequently, the same drug regimen was tested in stable diabetic patients in the ISAR-SWEET study. Although the study was underpowered, no benefit from abciximab was detected.[11] As reported above, ISAR-REACT-2—enrolling high-risk ACS patients—demonstrated for the first time that the administration of GP IIb/IIIa blockers was associated with a reduction in ischaemic events in patients optimally pre-treated with clopidogrel. At 30 days, a pre-specified analysis showed that the significant benefit was confined to troponin-positive patients. This is not surprising, since troponin-negative patients enrolled in ISAR-REACT-2 had an event rate at 30 days comparable with the overall population enrolled in the ISAR-REACT study.

The third field of GP IIb/IIIa inhibitor clinical trial testing included patients with ST-elevation myocardial infarction (STEMI). The largest trial, the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC), did not show a benefit of abciximab over placebo in patients undergoing PCI.[12] The study had the limitation that half of the patients did not receive a stent and—more importantly—that randomization occurred following coronary angiography. This resulted in the enrolment of a low-risk population, as demonstrated by an overall mortality rate of 1.4% at 30 days. Conversely, high-risk patients enrolled in smaller STEMI trials derived a benefit in terms of death or MI and death at 3 years.[13] A meta-analysis aiming to summarize the entire randomized experience on the intravenous administration of GP IIb/IIIa receptor antagonists in patients undergoing PCI identified 21 randomized trials for a total of almost 24 000 patients.[14] Allocation to GP IIb/IIIa blockers was associated with a statistically significant mortality reduction of 28 and 20% at 30 days and 1 year, respectively. Minor but not major bleedings were more common in the active treatment arm.

According to the 2005 ESC PCI guidelines, GP IIb/IIIa inhibitors have a grade IIa recommendation for PCI in stable patients for complex lesions, or as bailout for periprocedural complications, and abciximab has the same recommendation for primary PCI.[15] In the setting of ACS, a grade IIa recommendation is given for these agents in the 2007 ESC guidelines for patients with intermediate to high-risk status undergoing early coronary angiography.[16] From a practical perspective, even in the golden era of GP IIb/IIIa blockers their global market share never surpassed 50%. The best days for this class of drugs appear to be over, with a rapidly shrinking proportion of patients who may derive incremental benefits from GP IIb/IIIa blockers. Accordingly, the broad use of clopidogrel pre-loading and the availability of an alternative antithrombotic regimen such as bivalirudin, fondaparinux, or prasugrel will probably confine GP II/IIIa blockers to bailout therapy for periprocedural complications of PCI and to the treatment of high-risk ACS patients, with or without ST-segment elevation.

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